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5,101,874

(54) Pharmaceutical Preparation for the Parenteral, Enteral and Dermal Administration of Virtually Insoluble Medicinal Substances and a Process for Its Production

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Abstract of the disclosure

Pharmaceutical preparation for the parenteral, enteral and dermal administration of virtually insoluble medicinal substances and a process for its production

- 5 A medicinal preparation is described which contains a medicinal substance which is virtually insoluble in water and lipophilic media and one or more physiologically tolerated amphosurfactant(s) which is/are water-soluble or soluble in water in a micellar-colloidal manner, which
- 10 substances are present in dissolved form in one or more physiologically tolerated, water-free and water-miscible solvent(s). This medicinal preparation is employed dermally, enterally or via the buccal route, or, after the addition of water or water-containing solutions,
- 15 parenterally, enterally or via the buccal route.

Descripti n

Pharmac utical preparation for the parent ral, enteral and dermal administration f virtually insolubl medicinal substances and a process for its production

5 The invention relates to a medicinal preparation contain-
ing a medicinal substance, which is virtually insoluble
in water and lypophilic media, and one or more physio-
logically tolerated amphosurfactant(s), which is/are
water-soluble or soluble in water in a micellar-colloidal
10 manner, which substances are present in dissolved form in
one or more physiologically tolerated water-free and
water-miscible solvent(s).

The medicinal preparation is a solution and is employed
parenterally, enterally or via the buccal route after
15 adding water or water-containing solutions. However, the
medicinal solution can also be employed dermally, via the
buccal route and enterally without adding water, i.e.
water-free.

Medicinal preparations of medicinal substances which are
20 difficultly soluble in water have already been described.

EP-B-0,256,285 describes preparations of medicinal
substances which are difficultly soluble in water, which
preparations are suitable for parenteral injection and
contain an oil phase (e.g. fatty acid triglyceride), an
25 emulsifier (e.g. soybean lecithin) and water. The medici-
nal preparations are suspensions/emulsions and are
administered as such. Due to the nature of the prepar-
ation process and the fact that i.v. administration to
30 humans is not permitted, these suspensions/emulsions are
only suitable to be used in animal experiments for
exploratory investigations of the activity of medicinal
substances which are difficultly soluble in water.

A medicinal preparation in the form of an emulsion

conc ntrate, bas d on an il component, two complex emulsifiers (HLB > 10 and HLB < 4) and a water-soluble c component (e.g. ethanol or 1,2-propanediol), is described in EP-A-0,539,319. The medicinal substance which is difficultly soluble in water is dissolved in this emulsion concentrate (so-called "microemulsion preconcentrate"). The water-free preparation is only suitable for the oral mode of administration (e.g. in the form of gelatin capsules).

10 In accordance with DE-A-4,129,309, medicinal substances which are difficultly soluble in water are dissolved with the aid of lipophilic alkylactams, non-ionic surface-active substances and water-miscible, pharmaceutically utilizable liquids. The water-free solution is administered orally either in gelatin capsules or following prior dispersion with water. Depending on the composition of the medicinal preparation, emulsions or microsuspensions are formed.

20 DE-A-2,730,570 relates to injection solutions of drugs which are poorly soluble or insoluble in water, which solutions are based purely on water, in combination with natural micelle formers (e.g. glycocholate) and phospholipids (e.g. egg lecithin).

25 The medicinal preparations are water-containing finished solutions which are stable in storage and which contain a very high content of surface-active substances. A high content of surface-active substances is undesirable in the case of a preparation for i.v. administration.

30 EP-A-0,488,142 describes a solvent-free preparation of active compound-containing liposomes from medicinal substances which are difficultly soluble in water using natural and synthetic phospholipids. The aqueous liposome dispersions are suitable for parenteral administration.

EP-A-0,467,838 describes the preparation of active

compound-containing liposomes from medicinal substances which are difficultly soluble in water using purely synthetic phospholipids and employing acetic acid as solvent, with subsequent neutralization. The preparation 5 contains water and is free from organic solvents.

However, liposome formulations are unsuitable for use as finished pharmaceuticals owing to the formation of lysophosphatidylcholines (hydrolysis of the phospholipids) and their 10 property of fusing to form larger structures (aggregation).

A process for preparing active compound-containing liposomes from water-soluble, biologically active compounds is described in EP-B-0,158,441. The active compound and the membrane lipid which is suitable for this 15 purpose are dissolved, where appropriate using auxiliary substances which are membrane-stabilizing or which promote permeability, such as, for example, cholesterol or fatty acid sorbitan esters, in a solvent which is miscible with water. In addition, a defined quantity of 20 water is added, depending on active compound and mode of administration. After further addition of so-called excess water, and under specific preparation conditions, liposomes are formed which contain biologically active compounds enclosed by the membrane lipid.

25 As is the case for all liposome or vesicular formulations, the water-containing compositions also suffer from the instabilities (e.g. hydrolysis and tendency to fuse) which have already been described. In addition to this, when physiologically tolerated solvents are used, 30 these compositions are completely unsuitable, owing to their low dissolving power, for employment with medicinal substances which are practically insoluble.

Water-containing and water-free preparations for the production of so-called solution aerosols are also 35 described in EP-B-0,158,441. Owing to the composition of

the final formulation (= a r s 1 formulation), any formation of liposomes can be ruled out, since the pressure-liquifiable fluoro- x chl x -hydrocarbons (F 12/F 114) dissolve the lipid which is required for the 5 liposome formation and thereby prevent liposome formation.

EP-A-0,475,160 relates to medicinal preparations of medicinal substances which are readily soluble and difficultly soluble in water, which preparations are 10 composed of a highly purified phospholipid (phosphatidyl-choline content > 95 %), surfactants, ethanol and water. These formulations are only suitable for the non-invasive administration of medicinal substances in the form of 15 liposome-like droplets which contain the medicinal substance. They too suffer from the stability problems which have already been described, resulting in restrictions with regard to their sale as finished pharmaceuticals.

20 The object underlying the invention was to make available a pharmaceutically utilizable system in the form of a finished pharmaceutical which makes possible both the parenteral and the enteral, dermal and buccal administration of medicinal substances which are virtually insoluble in water and lipophilic media.

25 Depending on the application, the following points were to be taken into consideration when achieving this object:

1. Parenteral application:

30 a) intravenous
in order to achieve a blood level which was sufficiently high for a meaningful assessment of toxicity and pharmacokinetic properties, it was necessary to improve the extremely low solubility in the blood (< 1 mcg/100 ml) of medicinal substances which

5 are virtually insoluble in water and lipophilic media while preventing recrystallizations, i.e. the formation of uncontrolled, large solid particles and agglomerates which (can) give rise to occlusions of the capillary vessels,

10 b) subcutaneous/intramuscular
it was necessary to improve the local compatibility, which was known to be poor, of medicinal substances which are virtually insoluble in water and lipophilic media.

15 2. Enteral application:

15 a) it was necessary to improve the absorption, which was known to be poor owing to their low solubility, of medicinal substances which are virtually insoluble in water and lipophilic media,

20 b) it was necessary to prevent the spontaneous recrystallization of medicinal substances, which are virtually insoluble in water and lipophilic media, from hydrophilic solutions which are miscible with gastric/intestinal juice following mixing with gastric/intestinal juice.

25 3. Dermal application:

25 it was necessary to increase the concentration gradient, which was known to be low, of medicinal substances which are practically insoluble in water and lipophilic media when penetrating the skin in association with dermal use.

30 4. Buccal application:

30 it was necessary to increase the adsorption/absorption, which was known to be low, of medicinal substances which are virtually insoluble in water

and lipophilic media in association with buccal use
(e.g. rinsing and gargling solutions).

The object described is achieved by a stable solution
having been found, which solution contains the medicinal
5 substance which is virtually insoluble in water and
lipophilic media, one or more physiologically tolerated
amphosurfactant(s) which is/are soluble in water or
soluble in water in a micellar-colloidal manner and one
10 or more physiologically tolerated, water-free and water-
miscible solvent(s), and which, after mixing with water,
forms a transiently stable (metastable) micellar-
colloidal dispersion, i.e. the administration form which
is suitable for parenteral and enteral administration.

The water-free medicinal preparation is designated below
15 as a dispersion concentrate (DC).

A lipophilic medium is understood to mean, for example,
a fatty acid triglyceride.

20 Virtually insoluble in water and lipophilic media denotes
that the solubility of the medicinal substance in water,
or in a lipophilic medium, is less than 0.001 %, prefer-
ably less than 0.00001 %.

An amphosurfactant which is soluble in water or soluble
in water in a micellar-colloidal manner is understood to
mean a natural amphosurfactant.

25 An amphosurfactant is a natural, physiologically toler-
ated amphotelyte, analogous to the endogenous "surfactant"
(cf. Mutschler, E., Arzneimittelwirkungen (Effects of
pharmaceuticals), 6th edition, Stuttgart 1991, and
Keidel, Wolf-Dieter, Physiologie (Physiology), 6th
30 Edition, Stuttgart/New York, 1988), which is soluble in
water or soluble in water in a micellar-colloidal manner.

Micellar-colloidal denotes that, when water is added,

both micelles and colloids are formed (0.1 to 500 nm).

Suitable physiologically tolerated, water-free and water-miscible solvents are, inter alia, aliphatic alcohols, glycerol ketal, lactams, N-alkyllactams, amino acid alkyl esters and aminoalcohol acyl esters.

The invention therefore relates to a medicinal preparation for parenteral, enteral, dermal or buccal administration containing a medicinal substance which is virtually insoluble in water and lipophilic media, wherein the medicinal substance is dissolved in a solution composed of one or more physiologically tolerated ampho-surfactant(s), which is/are soluble in water or soluble in water in a micellar-colloidal manner, and one or more physiologically tolerated, water-free and water-miscible solvent(s).

The solution according to the invention is a so-called dispersion concentrate and, after mixing with water, blood plasma, tissue fluid or digestive juices, spontaneously (without energy being supplied) forms metastable, micellar-colloidal dispersions which contain the medicinal substance which is virtually insoluble in water and lipophilic media dissolved in a micellar-colloidal manner or disseminated in a colloidally dispersed manner.

In each case depending on the mode of administration, the solution is in a suitable form for administration either in the undiluted state or following the addition of water which, where appropriate, contains buffering substances, taste correctives, a physiologically tolerated solvent which is miscible with water in any ratio, and/or a physiologically tolerated hydrophilic colloid which is soluble in water.

The invention further relates to a process for producing the medicinal preparation, wherein the medicinal

substance which is virtually insoluble in water and lipophilic media is dissolved, at room temperature or at an insignificantly higher temperature and while stirring, in the water-free solution of the amphoteric surfactant(s) and 5 in the water-free and water-miscible solvent(s).

When carrying out the process, it is expedient to exclude oxygen, i.e. the process is carried out, for example, under N_2 protective gas.

10 A temperature which is insignificantly higher denotes temperatures up to 50°C, in particular up to 30°C.

When carrying out the process according to the invention, a clear solution is formed which is physically stable in storage, i.e. even after standing for a relatively long period of time (> 1 year) under the customary storage 15 conditions (+5°C, +23°C, +40°C), no medicinal substance or auxiliary substance separates out from the solution.

20 The dispersion concentrate according to the invention preferably contains from 1 to 20 % of medicinal substance, from 1.0 to 50 %, in particular from 3.75 to 27.5 %, of amphoteric surfactant, and solvent to 100 % (the percentage values are percent by weight).

25 The proportions of the active compounds, amphoteric surfactants and solvents are varied within the given concentrations depending on requirements (i.e. dosage and solubility of the active compounds and auxiliary substances).

30 The medicinal preparation (= medicinal form) according to the invention makes it possible to market medicinal substances which are virtually insoluble in water and lipophilic media in the form of clear liquids which are stable in storage (cf. Table 1).

For parenteral use (i.v., i.m., s.c.), the clear solution according to the invention of the medicinal substance

which is virtually insoluble in water and lipophilic media is diluted, prior to injection, with a predetermined quantity of water which, where appropriate, contains the said further additions. The two liquids are 5 mixed by repeated gentle shaking. This results in formation of the actual homogeneous parenteral administration form (analogy with "parenteralia diluenda", German Pharmacopoeia 9). The dilution is effected in dependence on the active compound concentration in the dispersion concentrate, the dose of active compound 10 required and the volume being administered. After adding water, a homogeneous dispersion having a weak opalescence is spontaneously formed from the clear solution (DC). The dispersion is stable for the period of time until injection demanded for parenteralia diluenda (at least 15 2 hours), i.e. neither medicinal substance nor auxiliary substance(s) separate(s) out from the parenteral administration form, the micellar-colloidal dispersion (cf. Table 2).

20 If an enteral administration is envisaged, the clear dispersion concentrate according to the invention is poured, for example in order to obtain a monodose, into hard or soft gelatin capsules using known methods, and then taken orally. It is also possible to administer the 25 solution on sugar, for example. Drinking ampoules can also be filled with the necessary quantity of dispersion concentrate, which can be drunk after adding water.

If a dermal administration is envisaged, the clear dispersion concentrate according to the invention is 30 poured into containers which are suitable for the dermal administration, for example a glass bottle on which a metering pump is mounted or a plastic squeeze bottle, for example made of polyethylene, and applied dropwise, in accordance with the valid dosage instructions envisaged 35 for the active compound, to the intended skin area, and massaged gently into the skin.

If a buccal administration is envisaged, the clear dispersion concentration according to the invention is poured into containers which are suitable for the buccal administration, for example a glass bottle on which a dropper or metering pump is mounted or a plastic monodose container, for example made of polyethylene, and introduced, in accordance with the valid dosage instructions envisaged for the active compound, without adding water or else after adding water, into the buccal cavity, being employed as a rinsing or gargling solution with the aim of achieving buccal adsorption/absorption of the medicinal substance.

15 Special phospholipid mixtures of natural origin (soybean or egg) which have a phosphatidylcholine content of from 20 to 90 %, preferably of from 40 to 80 %, and which are soluble in water or are soluble in water in a micellar-colloidal manner, are employed as amphot surfactant.

20 In addition, these phospholipid mixtures can also contain phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, phosphatidylglycerol and free phosphatidic acids, such as, for example, the commercial products Epicholin 75°, Phospholipon 50° and Lipoïd 875°.

25 In principle, synthetic and semi-synthetic phosphatides may also be employed provided they possess the solution properties which have been described.

30 Suitable physiologically tolerated, water-free and water-miscible solvents are monohydric or polyhydric aliphatic alcohols, (e.g. ethanol, 1,1-iminodi-2-propanol or 1,2-propanediol) and/or ether alcohols (e.g. tetrahydrofurfuryl alcohol polyethylene glycol ethers (e.g. Glycofurofuran 75°)) and/or glycerol ketal (e.g. 2-dimethyl-4-oxymethyl-1,3-dioxolane (such as 'Solketal) and/or lactams (e.g. 2-ketopyrrolidines, such as 'Soluphor P) and/or N-alkyl-lactams (e.g. N-methylpyrrolidone) and/or N-acylamino acid alkyl esters, N-acylamino alcohol acyl esters,

acylamin alcohol esters or the corresponding quaternization product, or amino acid alkyl esters. Monohydric or polyhydric aliphatic alcohols, in particular 1,2-propanediol and tetrahydrofurfuryl alcohol 5 polyethylene glycol ethers (e.g. Glycofurool 75 and Tetrakylol[®]) are preferably employed.

All substances which are appropriate for enteral, parenteral, dermal and buccal applications, and which are virtually insoluble in water and lipophilic media (solubility preferably less than 0.00001 %), are suitable for 10 use as medicinal substances. Those which are particularly suitable are:

1. Anti-AIDS agents, such as protease inhibitors, e.g. 15 N,N' -bis[(2S-(1,1-dimethylethylsulfonylmethyl)-3-(1-naphthyl)-propionyl)-L-valyl]-2S,5S-diamino-1,6-diphenylhexane-3R,4R-diol (also designated as HBY 793) and 20 4-isopropoxy carbonyl-5-methoxy-3-methylthiomethyl-3,4-dihydroquinoxaline-2(1H)-thione (also designated as HBY 097)
2. Antirheumatic agents and antipsoriatic agents, such as 25 leflunomide, 2-cyano-3-hydroxy-N-(4-trifluoromethylphenyl)crotonamide and 2-cyano-3-hydroxy-3-cyclopropyl-N-(3-methyl-4-trifluoromethylphenyl)propanamide
3. Antimycotic agents, such as clotrimazole, miconazole, econazole, bifonazole, rilopirox, ketoconazole, and itraconazole.
- 30 4. Antidiabetic agents, such as glibenclamide, glimepiride.
5. Diuretic agents, such as furosemide and piretanide.

Medicinal substances which are sensitive to hydrolysis, for example medicinal substances of recombinant origin, e.g. hirudin and its structural analogs having the appropriate activity, are also particularly suitable for 5 use as medicinal substances.

The medicinal preparation may also contain additional auxiliary substances which must dissolve in the water-free, water-miscible solvent.

10 Examples of additional auxiliary substances which the dispersion concentrate can contain are hydrophilic colloid, in particular polyvinylpyrrolidone (e.g. 'Kollidon types), for example in a quantity of from 1 to 10 %.

15 Further examples of suitable auxiliary substances, apart from the hydrophilic colloid which have already been mentioned, are non-ionic, surface-active substances, e.g. polyethylene glycol glycerol triricinoleate (e.g. 'Cremophor EL) and/or ionic surface-active substances, e.g. 20 1,4-bis(2-ethylhexyl)sulfosuccinate Na (e.g. 'Aerosol OT).

If it is expedient to add further auxiliary substances, the process according to the invention is carried out as follows:

25 The water-free and water-miscible solvent(s) is/are homogeneously mixed and dissolved with the amfosurfactant and the remaining auxiliary substances, including the hydrophilic colloid as well; the medicinal substance which is virtually insoluble in water and lipophilic media is subsequently likewise dissolved in this mixture 30 while stirring/rotating.

As a rule, no further auxiliary substances are mandatory for the water-free and water-miscible dispersion concentrates. For this reason, the material loading is

extremely low in the case of enteral, dermal and buccal administration, and also, in particular, in the case of parenteral or buccal administration following dilution with water.

5 The water-free and water-miscible preparations are physiologically unobjectionable; they can be administered in precise doses and are stable in storage (cf. Table 2).

In order further to explain the invention, the following examples are cited:

10 Example 1: Preparation of dispersion concentrate (DC)
(General Instructions)

The medicinal preparation (DC) according to the invention comprises the components medicinal substance (= virtually insoluble in water and lipophilic media), the auxiliary substance A (= water-free solvent which is miscible with water in any ratio), the auxiliary substance B (= ampho-surfactant which is soluble in water or is soluble in water in a micellar-colloidal manner), and, where appropriate, the auxiliary substance C (= non-ionic or ionic surface-active substance which is soluble in water) and/or, where appropriate, the auxiliary substance D (= hydrophilic colloid which is soluble in water).

Auxiliary substance A is initially introduced into a preparation vessel which is suitable for preparing solutions, and the auxiliary substance B is introduced in portions while stirring. Depending on the temperature (max. +50°C) and the efficiency of the mixing and stirring equipment, a clear solution is formed within 1-2 hours.

25 30 After that, the auxiliary substances C and/or D are, where appropriate, added stepwise at room temperature. The clear auxiliary substance solution (ASS) is formed after about 1 hour.

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The medicinal substance is introduced into the ASS. A clear solution, the DC, is formed after a short while.

After that, a pressure filtration is carried out, at 2-
5 2.5 bar, through a polyamide membrane having a pore width
of 0.2 μ m. Subsequently, the primary packings, correspond-
ing to the mode of administration, are filled with the
solution. In the case of parenteral administration,
single-dose containers are filled with the DC, which is
sterilized (20 min., 120°C) in the final container (=
10 injection vial).

All operations are carried out with oxygen to a large
extent being excluded (use of N₂ protective gas).

Example	2	3	4	5
DC Components [mg/g]				
15 Medicinal substance: HBY 793	10.00	10.00	40.00	40.00
A: 1,2-Propanediol	740.00	-	-	-
A: Glycofurool 75	-	865.00	835.00	710.00
B: Epicholin 75	250.00	125.00	125.00	250.00

The medicinal preparation DC is stable in storage. Table
20 1 shows the medicinal substance stability and clarity
stability of formulations of different concentrations and
having been produced by different processes and with
different loadings in the final container.

Table 1 Medicinal substance stability

Example	3	4	4
	(sterilized 20 min., 121°C)		
DC content of medicinal substance (HPLC) [mg/100 mg] after 6 months			
5 Initial value	1.01	4.13	4.18
Refrigerator	-	-	3.98
RT	1.00	4.05	3.98
+40°C	-	4.02	3.97

Clarity stability

10 The dispersion concentrates remain clear under all the storage conditions (6 months in a refrigerator, at room temperature (RT) or at 40°C).

Example 6

Preparation of the parenteral administration form
15 (General Instructions)

The medicinal preparation (DC) contained in single-dose containers - preparation according to Example 1 - is, for parenteral administration, converted into the actual administration form using a prescribed volume of water.

20 A metastable, micellar-colloidal dispersion having an average particle diameter of about 150 nm and a size distribution in the range from 80 to 250 nm is rapidly constituted from the clear DC after repeated gentle shaking with the prescribed volume of water.

25 Depending on the concentration being used, and on the composition of the DC, the pH varies in a range from 5.6 to 6.4. The osmolality is about 500 mOsmol/kg.

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The administration form (= micellar-c 11oidal dispersion) conforms to the requirements for "solutions for injection" or "solutions for infusion" in accordance with German Pharmacopoeia 10.

5 Table 2 shows the chemical and physical stability after standing for 6 hours at room temperature.

10 The dispersion concentrates in Examples 7, 8 and 9 were prepared in accordance with Example 1, and converted into the administration forms of Examples 7, 8 and 9 in accordance with Example 6.

Table 2

		Example 7	Example 8	Example 9
	Component	DC or adminis- tration form [mg/v.]	DC or adminis- tration form [mg/v.]	DC or adminis- tration form [mg/v.]
5	Medicinal substance: HBY 793, 95.7 % strength	5.73	22.96	22.96
	B: Epicholin 75	69.50	69.50	69.50
	A: Glycofurool 75	480.77	463.54	463.54
	DC (mg/v.)	556.00	556.00	556.00
	Water	5000.00	5000.00	2222.75
10	Administration form	5556.00 (= 1 mg/ml)	5556.00 (= 4 mg/ml)	2778.75 (= 8 mg/ml)
	Content of active compound (HPLC) [mg/v.]			
	0 hours	5.89	23.56	22.78
	after 6 hours	5.83	23.56	22.92
15	Average particle diameter [nm, RT] ^a			
	0 hours	149.2	123.9	165.8
	after 6 hours	151.4	127.3	167.6
	Polydispersity [RT] ^a			
	0 hours	0.248	0.287	0.293
	after 6 hours	0.178	0.290	0.241

20 *) measured using a photon-correlation spectrometer
(Autosizer 2c, from Malvern)

v. denotes vial/final container

25 Table 3 shows the analysis of pharmacokinetic investigations following intravenous and subcutaneous administration of Examples 7 and 8 to the mouse.

The investigations were carried out as follows:

30 The preparations were administered intravenously, subcutaneously or orally, by gavage, to female NMRI mice aged about 6 weeks. At specified times, cardiac puncture was carried out, under anaesthesia, on in each case two or

three mice. The anaesthesia was achieved by the intraperitoneal administration of 0.3 ml of a urethan solution (0.2 mg/ml). The blood that was removed was stored at 4°C until it had coagulated and then centrifuged. The serum thus obtained was centrifuged once again to purify it (Eppendorff centrifuge, model 5414, 5 min.). The serum was stored at -20°C until it was analyzed.

The samples were analyzed using HPLC, with an ether extraction first being carried out in the case of HBY 793 analysis. The content was determined by fluorometry.

Table 3

Mode of administration	Example	Dose [mg/kg]	AUC [ng x h/ml]	AUC/Dose	t/2 [min.]
i.v.	7	8.4	2932	301	221
	8	50.0	6699	134	78 [hours]
	7	4.1	347	84	2.2
s.c.	8	16.3	469	28	2.9

AUC = Area under the curve

Table 3 shows that complete absorption does not occur in the case of s.c. administration (standardization: i.v. administration = 100 % bioavailability).

Local compatibility is good under all test conditions.

The dispersion concentrates of Examples 10 to 14 are prepared in analogy with Example 1.

Example	10	11	12	13
DC Components [mg/g]				
Medicinal substance:	10.00	10.00	10.00	30.00
HBY 793				
5 A: 1,2-Propanediol	490.00	865.00	-	-
A: Glycofurool 75	-	-	928.00	845.00
B: Epicholin 75	250.00	62.50	46.50	62.50
C: PEG-7-glycerylcocoate	250.00	-	-	-
C: Cremophor EL	-	62.50	15.50	62.50

Example	14	15	16	17
DC Components [mg/g]				
Medicinal substance:	40.00	40.00	40.00	50.00
HBY 793				
15 A: Glycofurool 75	785.00	797.50	723.00	725.00
B: Epicholin 75	125.00	62.50	93.500	125.00
C: Cremophor EL	-	-	93.50	-
D: Kollidon 17 (PVP)	50.00	100.00	50.00	100.00

Table 4 shows the analysis of pharmacokinetic investigations carried out on formulations containing auxiliary substances of the groups C) and D) following intravenous administration to the mouse (experimental description; cf. investigations of Examples 7 and 8). The concentration (C) of active compound was ascertained after 60 minutes.

Table 4

Mode of administration	Example	Dose [mg/kg]	C, 60 min. [ng/ml]	AUC [ngxh/ml]
i.v.	10	9.9	196	851
i.v.	13	29.7	8049	6297
i.v.	17	32.5	1073	-

Local compatibility is good.

Table 5 shows the pharmacokinetic analyses carried out on formulations having different medicinal substance/auxiliary substance ratios following subcutaneous administration to the mouse (experimental description; cf. investigations on Examples 7 and 8).

Table 5

Example	Medicinal substance/auxiliary substance ratio (parts) Medicinal substance: B) : D)	Dose [mg/kg]	AUD [ngxh/ml]	AUD/Dose
4	1 : 3.125 : -	20	1818	90.9
15	1 : 1.560 : 2.5	20	1815	92.6
5	1 : 6.250 : -	40	3627	90.7
15	1 : 1.560 : 2.5	33	3219	96.7

AUD = area under the data

20 The dispersion concentrates of Examples 18 to 24 were prepared in analogy with Example 1.

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Example	18	19	20	21	
DC components [mg/g]					
Medicinal substance:					
	HBY 097	20.00	20.00	20.00	50.00
5	A: Glycofurool 75	855.00	792.50	817.50	762.50
	B: Epicholin 75	125.00	93.75	62.50	93.75
	C: Cremophor EL	-	93.75	-	93.75
	D: Kollidon 17 (PVP)	-	-	100.00	-

Example	22	23	24	
DC Components [mg/g]				
Medicinal substance: HBY 097				
10	50.00	100.00	200.00	
	A: 1,2-Propanediol	762.50	-	-
	A: Glycofurool 75	-	618.75	518.75
	B: Epicholin 75	93.75	93.75	93.75
15	C: Cremophor EL	93.75	-	187.50
	C: Cremophor RH 40	-	187.50	-

Table 6 shows pharmacokinetic analyses carried out on different formulations containing the medicinal substance HBY 097 which were administered to different animal species using different modes of administration.

The investigations in the mouse were carried out as indicated under Examples 7 and 8. The tests were carried out on the dog as follows.

Dog:

25 Male dogs (beagles), having a bodyweight of about 20 kg, were placed in individual cages approximately 16 hours before beginning the experiment. Until the end of the experiment, the animals were not given any feed but had unrestricted access to drinking water. In the case of the 30 oral administration, the dogs were in each case given the

test preparation in capsules, which were pushed deep into the pharynx. The dose was rinsed down with approximately 20 ml of tap water using a 20 ml syringe.

5 Intravenous administration of test preparations was effected by injecting them into the antibrachial cephalic vein, care being taken to ensure that this same vein was not used during the experiment for removing blood samples.

10 At the scheduled times, 5-8 ml of blood were in each case collected in heparinized sampling tubes by puncturing the antibrachial cephalic vein. The samples were placed in an ice bath for about 1 hour and then centrifuged (10 min., 3,000 rpm at 4°C). The heparinized plasma was centrifuged once more to purify it and subsequently stored at -20°C
15 until it was analyzed.

Analysis

20 The samples were analyzed by HPLC, with a precipitation with acetonitrile being carried out before analyzing for HBY 097. The content was determined by measuring the UV absorption.

Table 6

Animal Species	Mode of administration	Example	Dose [mg/kg]	AUC [ng·h/ml]
Mouse	i.v.	19	7.4	668
			16.0	2703
	p.o.	22	100.0	2322
			100.0	4275
25 Dog	i.v.	23	5.3	6188
		19	1.7	925
	i.v.		2.0	956

The dispersion concentrates of Examples 25 to 41 were prepared in analogy with Example 1.

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Example	25	26	27	28
DC components [mg/g]				
Rilopirox, dermal	10.00	10.00	-	-
Leflunomide, dermal	-	-	10.00	10.00
5 A: 1,2-Propanediol	-	-	740.00	740.00
A: Glycofurool 75	865.00	740.00	-	-
B: Epicholin 75	125.00	-	250.00	187.50
B: Lipoïd S 75	-	187.50	-	-
C: Cremophor RH 40	-	62.50	-	62.50

Example	29	30	31	32	33	34
DC components [mg/g]						
Glimepiride, p.o.	10.0	15.0	-	-	-	-
Itraconazole, i.v.	-	-	5.0	5.0	5.0	5.0
15 A: 1,2-Propanediol	807.5	-	-	-	-	-
A: Glycofurool 75	-	685.0	745.0	770.0	870.0	682.5
B: Epicholin 75	-	-	250.0	125.0	125.0	125.0
B: Phospholipon 50 ^R	62.5	-	-	-	-	-
B: Lipoïd S 75	-	125.00	-	-	-	-
C: Cremophor RH 40	-	125.00	-	-	-	187.5
20 C: Myrij S2	95.00	-	-	-	-	-
C: Dioctyl-sulfosuccinate	25.00	-	-	-	-	-
D: Kollidon 17 (PVP)	-	50.00	-	100.00	-	-

Example	35	36	37
DC components [mg/g]			
2-Cyano-3-hydroxy-N-(4-trifluoro-methylphenyl)crotonamide	10.0 mg	50.0 mg	50.0 mg
5 A: 1,1-Iminodi-2-propanol	-	50.0 mg	50.0 mg
A: Glycofurool 75	740.0 mg	-	-
A: 1,2-Propanediol	-	775.0 mg	650.0 mg
B: Lipoid S 75	250.0 mg	125.0 mg	250.0 mg

Example	38	39	40	41
DC components [mg/g]				
10 Furosemide	15.0 mg	10.0 mg	-	-
Piretanide	-	-	5.0 mg	5.0 mg
A: Glycofurool 75	685.0 mg	740.0 mg	770.0 mg	870.0 mg
B: Epicholin 75	-	250.0 mg	125.0 mg	125.0 mg
15 B: Lipoid S 75	125.0 mg	-	-	-
C: Cremophor RH 40	125.0 mg	-	-	-
D: Kollidon 17/PVP	50.0 mg	-	100.0 mg	-

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A medicinal preparation for parenteral, enteral, dermal or buccal administration containing a medicinal substance which is virtually insoluble in water and lipophilic media, wherein the medicinal substance is dissolved in a solution composed of one or more physiologically tolerated amphoteric surfactant(s), which is/are soluble in water or soluble in water in a micellar-colloidal manner, and one or more physiologically tolerated, water-free and water-miscible solvent(s).
5
2. The medicinal preparation as claimed in claim 1, which contains further physiologically tolerated auxiliary substances which are soluble in the water-free, water-miscible solvent.
10
3. The medicinal preparation as claimed in claim 1, which additionally contains a physiologically tolerated hydrophilic colloid, and/or physiologically tolerated, non-ionic or ionic, surface-active substances.
15
4. The medicinal preparation as claimed in claim 1, wherein the amphoteric surfactant is a phospholipid mixture having a phosphatidylcholine content of from 40 to 80 %, and the solvent is 1,2-propanediol or tetrahydrofurfuryl alcohol polyethylene glycol ether.
20
5. The medicinal preparation as claimed in claim 1, wherein the medicinal substance is an anti-AIDS agent, an antirheumatic agent, an antipsoriatic agent, a diuretic agent, an antimycotic agent or an antidiabetic agent.
25
6. Water-containing dispersion for the parenteral, enteral or buccal administration of medicinal
30

substances which are virtually insoluble in water or lipophilic media, wherein the medicinal preparation as claimed in one of claims 1 to 5 additionally contains water which, where appropriate, contains physiologically tolerated buffering substances, taste correctives, a physiologically tolerated solvent which is miscible with water in any ratio, and/or a physiologically tolerated, hydrophilic colloid which is soluble in water.

10 7. A process for producing a medicinal preparation as claimed in claim 1, wherein the medicinal substance which is virtually insoluble in water and lipophilic media is dissolved, at room temperature or at a temperature which is insignificantly higher, in the water-free solution of the amphoteric(s) and the water-free and water-miscible solvent(s).

15 8. A process for producing a water-containing dispersion as claimed in claim 6, wherein a medicinal preparation as claimed in one of claims 1 to 5 is dispersed in water which, where appropriate, contains physiologically tolerated buffering substances, taste correctives, a physiologically tolerated solvent which is miscible with water in any ratio, and/or a physiologically tolerated, hydrophilic colloid which is soluble in water.

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